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Higher Therapeutic Index *in vivo* with Radiolabeled Somatostatin Receptor Antagonists May Broaden the Safety Window of PRRT

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Background: Radiolabeled somatostatin (sst) receptor antagonists have been recently introduced in the clinic for treatment (PRRT) and imaging of neuroendocrine tumors. The therapeutic index, imaging contrast as well as the influence of the mass of OPS201 (a novel radiolabeled sst antagonist) is not known.

Methods: The sst2-antagonist ^{177}Lu-OPS201 and the sst2-agonist ^{177}Lu-DOTATATE were compared head-to-head in 2 sst2-expressing xenograft models (HEK-hsst2 and AR42J) *in vivo*. Biodistribution, pharmacokinetic and nano SPECT/CT imaging studies were performed. Influence of increasing peptide mass and use of octreotide were investigated in a theranostic approach.

Results: Besides a usual physiological pattern of uptake in the sst2-receptor expressing organs, the antagonist showed higher uptake (e.g. ~35% at 4h, $p<0.05$) and longer residence time in tumor in comparison with agonist (19.1h vs 7.5h) resulting in a 2.5 times higher tumor dose. The antagonist had higher kidney uptake, however the therapeutic index, defined as tumour-to-kidney dose ratio, remained by 34% in favor of ^{177}Lu-OPS201.

Increasing the mass of ^{177}Lu-OPS201 from 10 to 2000 pmol caused no relevant saturation in the HEK-hsst2 tumor (19-24%IA/g, at 4h, p>0.05) but reduced significantly the background, except renal uptake (see nanoSPECT/CT images below). The improved image contrast and therapeutic index were confirmed with increased mass of ^{177}Lu-OPS201 (from 10 to 200pmol) in AR42J xenografts. However tumor uptake significantly decreased after injecting 2000pmol. Co- and pre-injection of 200-fold excess of octreotide i.v. did not modify the distribution of the antagonist, including the tumor uptake.

Conclusion: The increased tumor uptake, prolonged tumor residence time as well as the more favorable differential washout of ^{177}Lu-OPS201 improve the therapeutic index compared to ^{177}Lu-DOTATATE. An optimized antagonist-mass will likely further reduce liver and bone marrow toxicity, while interrupting sst-analogs before PRRT may not any longer be needed with radiolabeled antagonists.